

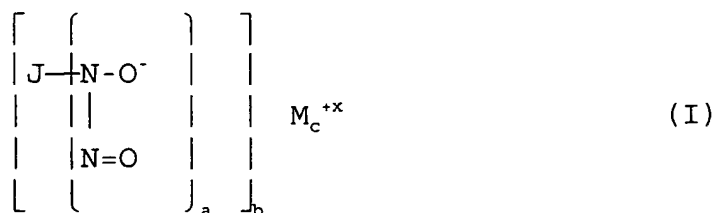
PENDING CLAIMS

U.S. SERIAL NO. 08/837,812

BIOPOLYMER-BOUND NITRIC OXIDE-RELEASING COMPOSITIONS, PHARMACEUTICAL COMPOSTIONS INCORPORATING SAME AND METHODS OF TREATING BIOLOGICAL DISORDERS USING SAME

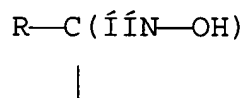
1. A polymeric composition capable of releasing nitric oxide, said composition comprising (i) a biopolymeric backbone wherein said backbone is of a tissue-specific antibody or fragment thereof, a cell-specific antibody or fragment thereof, a tumor-specific antibody or fragment thereof, a protein containing a recognition sequence for a receptor-ligand interaction favorable to cell or tissue selective attachment, an anti-chemotactic agent, or a hormone, wherein said backbone includes at least one amino group or at least one carboxyl group or combinations thereof, and (ii) at least one nitric oxide-releasing $N_2O_2^-$ functional group selected from the group consisting of $X\{N(O)NO\}$ and $[N(O)NO\}X$, wherein X is an organic moiety covalently bonded to said $[N_2O_2]$, and wherein the $[N_2O_2]$ group is covalently bonded in said polymeric composition at one or more of said amino group or said carboxyl group through said organic moiety X.

5. The polymeric composition of claim 1, wherein said nitric oxide-releasing $N_2O_2^-$ functional group is of the formula:



wherein J is an inorganic moiety or an organic moiety selected from the group consisting of C_1 - C_{12} aliphatic, C_3 - C_8 cycloalkyl,

benzyl, phenyl, substituted benzyl, substituted phenyl, benzylcarbonyl, phenylcarbonyl, substituted benzylcarbonyl, substituted phenylcarbonyl, C₁-C₁₂ acyl, and

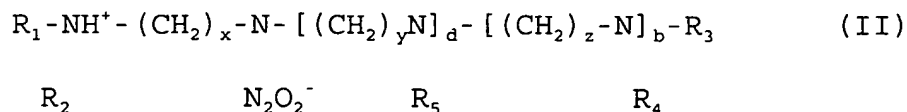


wherein R is C₁-C₁₂ aliphatic, C₃-C₈ cycloalkyl, benzyl, phenyl, substituted benzyl or substituted phenyl, and said substituted benzyl and substituted phenyl is substituted with one or two substituents selected from the group consisting of halogen, hydroxy, C₁-C₄ alkyl, C₁-C₄ alkoxy, amino, mono C₁-C₄ alkylamino, di C₁-C₄ alkyl-amino, phenyl and phenoxy, M^{+x} is a pharmaceutically acceptable cation, where x is the valence of the cation, a is one or two, and b and c are the smallest integers that result in a neutral compound.

6. The method of claim 5, wherein J is a moiety which is linked to the nitrogen of the remainder of the complex through an atom other than a carbon atom.

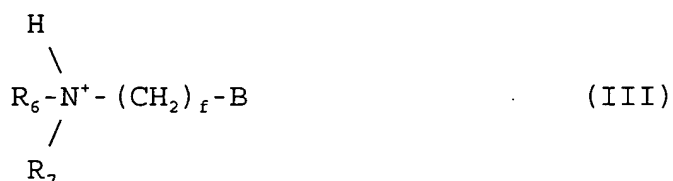
7. The polymeric composition of claim 5, wherein the nitric-oxide releasing group is a compound other than a salt of alanosine or dopastin.

8. The polymeric composition of claim 1, wherein said nitric oxide-releasing N₂O₂⁻ functional group is of the formula:



wherein b and d are the same or different and may be zero or one, R_1 , R_2 , R_3 , R_4 , and R_5 are the same or different and may be hydrogen, C_{3-8} cycloalkyl, C_{1-12} straight or branched chain alkyl, benzyl, benzoyl, phthaloyl, acetyl, trifluoroacetyl, p-toluyyl, t-butoxycarbonyl, or 2,2,2-trichloro-t-butoxycarbonyl, and x, y, and z are the same or different and are integers from 2 to 12.

9. The polymeric composition of claim 1, wherein said nitric oxide-releasing $N_2O_2^-$ functional group is of the formula:



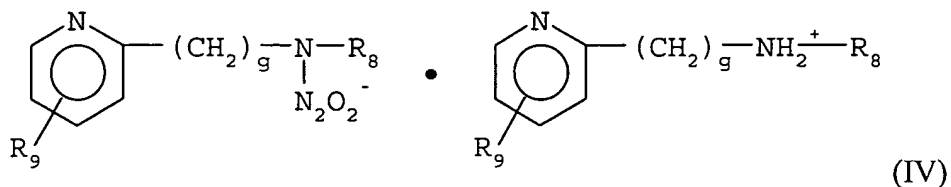
wherein B is $N_2O_2^-$ or $N_2O_2^-$,

R_6 and R_7 are the same or different and may be hydrogen, C_{3-8} cycloalkyl, C_{1-12} straight or branched chain alkyl, benzyl, benzoyl, phthaloyl, acetyl, trifluoroacetyl, p-toluyyl, t-butoxycarbonyl, or 2,2,2-trichloro-t-butoxycarbonyl, f is an integer from 0 to 12, with the proviso that when B is the substituted piperazine moiety



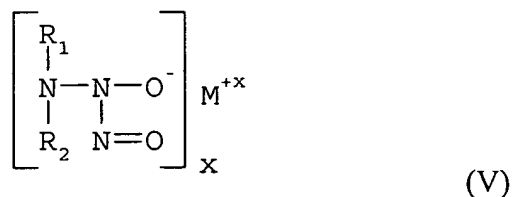
then f is an integer from 2 to 12.

10. The polymeric composition of claim 1, wherein said nitric oxide-releasing N_2O_2^- functional group is of the formula:



wherein R_8 is hydrogen, C_{3-8} cycloalkyl, C_{1-12} straight or branched chain alkyl, benzyl, benzoyl, phthaloyl, acetyl, trifluoroacetyl, p-toluy, t-butoxycarbonyl, or 2,2,2-trichloro-t-butoxycarbonyl, R_9 is hydrogen or a C_1 - C_{12} straight or branched chain alkyl, and g is 2 to 6.

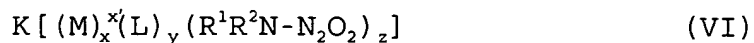
11. The polymeric composition of claim 1, wherein said nitric oxide-releasing N_2O_2^- functional group is of the formula:



wherein R_1 and R_2 are independently selected from the group consisting of a straight chain or branched chain C_1 - C_{12} alkyl group and a benzyl group, or else R_1 and R_2 together with the nitrogen atom they are bonded to form a heterocyclic group, a pyrrolidino, piperidino, piperazino or morpholino group, $\text{M}^{+\text{x}}$ is

a pharmaceutically acceptable cation, and x is the valence of the cation.

12. The polymeric composition of claim 1, wherein said nitric oxide-releasing $N_2O_2^-$ functional group is of the formula:



wherein M is a pharmaceutically acceptable metal, or, where x is at least two, a mixture of two different pharmaceutically acceptable metals, L is a ligand different from $(R^1R^2N-N_2O_2)$ and is bound to at least one metal, R^1 and R^2 are each organic moieties and may be the same or different, x is an integer of from 1 to 10, x' is the formal oxidation state of the metal M, and is an integer of from 1 to 6, y is an integer of from 1 to 18, and where y is at least 2, the ligands L may be the same or different, z is an integer of from 1 to 20, and K is a pharmaceutically acceptable counterion to render the compound neutral to the extent necessary.

13. The polymeric composition of claim 1, wherein said nitric oxide-releasing $N_2O_2^-$ functional group is of the formula:



wherein R is C_{2-8} lower alkyl, phenyl, benzyl, or C_{3-8} cycloalkyl, any of which R groups may be substituted by one to three substituents, which are the same or different, selected from the group consisting of halo, hydroxy, C_{1-8} alkoxy, $-NH_2$, $-C(O)NH_2$, $-CH(O)$, $-C(O)OH$, and $-NO_2$, X is a

pharmaceutically acceptable cation, a pharmaceutically acceptable metal center, or a pharmaceutically acceptable organic group selected from the group consisting of C₁₋₈ lower alkyl, -C(O)CH₃, and -C(O)NH₂, and y is one to three, consistent with the valence of X.

14. The polymeric composition of claim 1, wherein said nitric oxide-releasing N₂O₂⁻ functional group is of the formula:



wherein R₁ and R₂ are independently chosen from C₁₋₁₂ straight chain alkyl, C₁₋₁₂ alkoxy or acyloxy substituted straight chain alkyl, C₂₋₁₂ hydroxy or halo substituted straight chain alkyl, C₃₋₁₂ branched chain alkyl, C₃₋₁₂ hydroxy, halo, alkoxy, or acyloxy substituted branched chain alkyl, C₃₋₁₂ straight chain olefinic and C₃₋₁₂ branched chain olefinic which are unsubstituted or substituted with hydroxy, alkoxy, acyloxy, halo or benzyl, or R₁ and R₂ together with the nitrogen atom to which they are bonded form a heterocyclic group, a pyrrolidino, piperidino, piperazino or morpholino group, and R₃ is a group selected from C₁₋₁₂ straight chain and C₃₋₁₂ branched chain alkyl which are unsubstituted or substituted by hydroxy, halo, acyloxy or alkoxy, C₂₋₁₂ straight chain or C₃₋₁₂ branched chain olefinic which are unsubstituted or substituted by halo, alkoxy, acyloxy or hydroxy, C₁₋₁₂ unsubstituted or substituted acyl, sulfonyl and carboxamido; or R₃ is a group of the formula -(CH₂)_n-ON=N(O)NR₁R₂, wherein n is an integer of 2-8, and R₁ and R₂ are as defined above; with

the proviso that R_1 , R_2 and R_3 do not contain a halo or a hydroxy substituent α to a heteroatom.

15. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the polymeric composition of claim 1.

19. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the polymeric composition of claim 5.

20. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the polymeric composition of claim 6.

21. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the polymeric composition of claim 7.

22. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the polymeric composition of claim 8.

23. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the polymeric composition of claim 9.

24. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the polymeric composition of claim 10.

25. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the polymeric composition of claim 11.

26. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the polymeric composition of claim 12.

27. A method of treating a biological disorder in a mammal in which dosage with nitric oxide is therapeutic, comprising administering to said mammal a polymeric composition capable of releasing nitric oxide, said composition comprising a biopolymeric backbone wherein said backbone is of a protein, wherein said backbone includes at least one amino group or at least one carboxyl group or combinations thereof, and a nitric oxide-releasing $N_2O_2^-$ functional group bound to said biopolymer at one or more of said amino group or said carboxyl group, in an amount sufficient to release a therapeutically effective amount of nitric oxide.

31. A method of treating a biological disorder in a mammal in which dosage with nitric oxide is therapeutic, comprising administering the polymeric composition of claim 5 in an amount sufficient to release a therapeutically effective amount of nitric oxide.

32. A method of treating a biological disorder in a mammal in which dosage with nitric oxide is therapeutic, comprising administering the polymeric composition of claim 6 in an amount sufficient to release a therapeutically effective amount of nitric oxide.

33. A method of treating a biological disorder in a mammal in which dosage with nitric oxide is therapeutic, comprising administering the polymeric composition of claim 7 in an amount sufficient to release a therapeutically effective amount of nitric oxide.

34. A method of treating a biological disorder in a mammal in which dosage with nitric oxide is therapeutic, comprising administering the polymeric composition of claim 8 in an amount sufficient to release a therapeutically effective amount of nitric oxide.

35. A method of treating a biological disorder in a mammal in which dosage with nitric oxide is therapeutic, comprising administering the polymeric composition of claim 9 in an amount sufficient to release a therapeutically effective amount of nitric oxide.

36. A method of treating a biological disorder in a mammal in which dosage with nitric oxide is therapeutic, comprising administering the polymeric composition of claim 10 in an amount sufficient to release a therapeutically effective amount of nitric oxide.

37. A method of treating a biological disorder in a mammal in which dosage with nitric oxide is therapeutic, comprising administering the polymeric composition of claim 11 in an amount sufficient to release a therapeutically effective amount of nitric oxide.

38. A method of treating a biological disorder in a mammal in which dosage with nitric oxide is therapeutic, comprising administering the polymeric composition of claim 12 in an amount sufficient to release a therapeutically effective amount of nitric oxide.

39. A method of treating a biological disorder in a mammal in which dosage with nitric oxide is therapeutic, comprising administering to said mammal the polymeric composition of claim 1 in an amount sufficient to release a therapeutically effective amount of nitric oxide.